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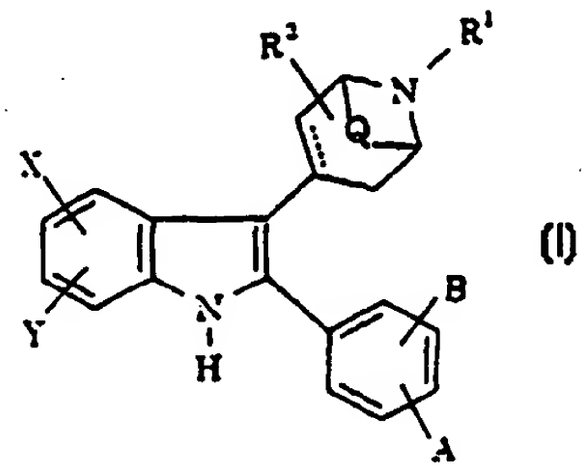
(54) Title: AZABICYCLE–SUBSTITUTED PHENYLINDOLE DERIVATIVES AS LIGANDS FOR 5–HT2A RECEPTORS

(57) Abstract

Compounds of formula (I), or a salt thereof wherein the broken line represents an optional chemical bond; A and B independently represent hydrogen, halogen, cyano, nitro, trifluoromethyl, trifluoromethoxy; C_{1-6}alkyl or C_{1-6}alkoxy; or A and B, when attached to adjacent carbon atoms, together represent methylenedioxy; X and Y independently represent hydrogen, halogen, trifluoromethyl, trifluoromethoxy, C_{1-6}alkyl, C_{1-6}alkoxy or phenyl; Q represents a group of the formula $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$; R^1 represents hydrogen, C_{1-6}alkyl, or an optionally substituted aryl(C_{1-6})alkyl, heteroaryl(C_{1-6})alkyl or C_{3-7}heterocycloalkyl(C_{1-6})alkyl group; and R^2 represents hydrogen, halogen. C_{1-6}alkyl, hydroxy or C_{1-6}alkoxy are selective antagonists of the human 5–HT_{2A} receptor and are therefore useful as pharmaceutical agents, especially in the treatment and/or prevention of adverse conditions of the central nervous system, including psychotic disorders such as schizophrenia.



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AZABICYCLE-SUBSTITUTED PHENYLINDOLE DERIVATIVES AS LIGANDS FOR 5-HT2A RECEPTORS

The present invention relates to a class of indole derivatives which act on serotonin receptors (also known as 5-hydroxytryptamine or 5-HT receptors). More particularly, the invention concerns 1*H*-indole derivatives bearing an optionally substituted phenyl ring at the 2-position of the indole moiety and an azabicyclic ring system at the 3-position of the indole moiety. These compounds are selective antagonists of the human 5-HT_{2A} receptor and are therefore useful as pharmaceutical agents, especially in the treatment and/or prevention of adverse conditions of the central nervous system, including psychotic disorders such as schizophrenia.

Schizophrenia is a disorder which is conventionally treated with drugs known as neuroleptics. In many cases, the symptoms of schizophrenia can be treated successfully with so-called "classical" neuroleptic agents such as haloperidol. Classical neuroleptics generally are antagonists at dopamine D_2 receptors.

Notwithstanding their beneficial antipsychotic effects, classical neuroleptic agents such as haloperidol are frequently responsible for eliciting acute extrapyramidal symptoms (movement disorders) and neuroendocrine (hormonal) disturbances. These side-effects, which plainly detract from the clinical desirability of classical neuroleptics, are believed to be attributable to D_2 receptor blockade in the striatal region of the brain.

The compound (+)-α-(2,3-dimethoxyphenyl)-1-[2-(4-fluorophenyl)-ethyl]-4-piperidinemethanol (also known as MDL-100,907) is described in WO 91/18602. In preclinical studies, MDL-100,907 failed to induce catalepsy and failed to block apomorphine-induced stereotyped behaviour in animal models, strongly suggesting that this compound would be free from any liability to cause extrapyramidal side-effects. MDL-100,907 is

currently undergoing clinical trials in schizophrenic patients and has demonstrated efficacy in a multicentre, placebo-controlled study for antipsychotic potential, with no neurological adverse effects. Pharmacologically, MDL-100,907 has been shown to be a potent antagonist of human 5-HT_{2A} receptors, whilst being essentially devoid of activity at the human dopamine D_2 receptor. It is accordingly believed that compounds which can interact selectively with the 5-HT_{2A} receptor relative to the dopamine D_2 receptor will display the beneficial level of antipsychotic activity associated with 5-HT_{2A} receptor antagonism, whilst minimizing or even avoiding the extrapyramidal and other side-effects arising from an interaction with dopamine D_2 receptors.

The compounds of the present invention are potent antagonists of the human 5-HT_{2A} receptor, and are accordingly of benefit in the treatment and/or prevention of psychotic disorders such as schizophrenia. The compounds of the invention display more effective binding to the human 5-HT_{2A} receptor than to the human dopamine D_2 receptor, and they can therefore be expected to manifest fewer side-effects than compounds which do not discriminate in their binding affinity as between 5-HT_{2A} and D_2 receptors.

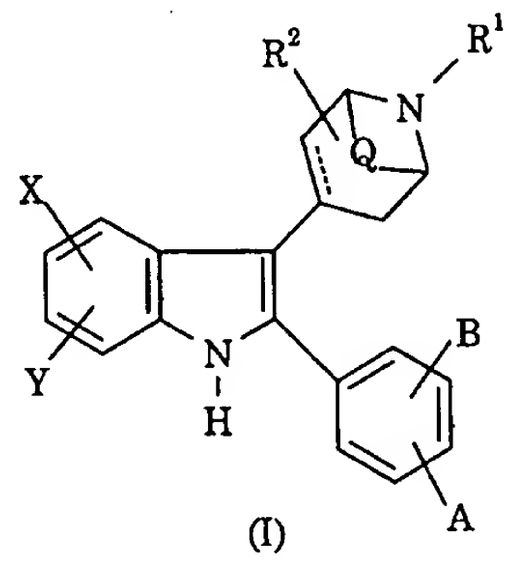
By virtue of their potent human 5-HT_{2A} receptor antagonist activity, the compounds of the present invention are also effective in the treatment of neurological conditions including depression, anxiety, panic disorder, obsessive-compulsive disorder, pain, sleep disorders such as insomnia, eating disorders such as anorexia nervosa, and dependency or acute toxicity associated with narcotic agents such as LSD or MDMA; and cardiovascular conditions including variant angina, Raynaud's phenomenon, intermittent claudication, coronary and peripheral vasospasms, fibromyalgia, cardiac arrhythmias and thrombotic illness. They may also be generally of benefit in the inhibition of platelet aggregation, as well as in controlling the extrapyramidal symptoms associated with the administration of neuroleptic agents. They may

further be effective in the lowering of intraocular pressure and may therefore be beneficial in treating glaucoma (cf. T. Mano *et al.* and H. Takaneka *et al.*, *Investigative Ophthalmology and Visual Science*, 1995, Vol. 36, pages 719 and 734 respectively).

Being 5-HT_{2A} receptor antagonists, the compounds of the present invention may also be beneficial in preventing or reducing the toxic symptoms associated with the intake of ergovaline in animals consuming *Acremonium coenophialum* infected tall fescue (cf. D. C. Dyer, *Life Sciences*, 1993, **53**, 223-228).

The compounds according to the present invention are potent and selective 5-HT_{2A} receptor antagonists having a human 5-HT_{2A} receptor binding affinity (K_i) of 100 nM or less, typically of 50 nM or less and preferably of 10 nM or less. The compounds of the invention may possess at least a 10-fold selective affinity, suitably at least a 20-fold selective affinity and preferably at least a 50-fold selective affinity, for the human 5-HT_{2A} receptor relative to the human dopamine D_2 receptor.

The present invention provides a compound of formula I, or a salt thereof:



(I)

wherein the broken line represents an optional chemical bond;

A and B independently represent hydrogen, halogen, cyano, nitro, trifluoromethyl, trifluoromethoxy, C_{1-6} alkyl or C_{1-6} alkoxy; or A and B,

when attached to adjacent carbon atoms, together represent methylenedioxy;

X and Y independently represent hydrogen, halogen, trifluoromethyl, trifluoromethoxy, C_{1-6} alkyl, C_{1-6} alkoxy or phenyl;

Q represents a group of formula $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$;

R^1 represents hydrogen, C_{1-6} alkyl, or an optionally substituted aryl(C_{1-6})alkyl, heteroaryl(C_{1-6})alkyl or C_{3-7} heterocycloalkyl(C_{1-6})alkyl group; and

R^2 represents hydrogen, halogen, C_{1-6} alkyl, hydroxy or C_{1-6} alkoxy.

Where R^1 represents aryl(C_{1-6})alkyl, heteroaryl(C_{1-6})alkyl or C_{3-7} heterocycloalkyl(C_{1-6})alkyl, this group may be optionally substituted by one or more substituents. Suitably, the group R^1 is unsubstituted, or substituted by one or two substituents. In general, the group R^1 may be unsubstituted or monosubstituted. Examples of optional substituents on the group R^1 include halogen, cyano, trifluoromethyl, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{2-6} alkoxycarbonyl, C_{2-6} alkylcarbonyl, C_{1-6} alkylsulphonyl, arylsulphonyl, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, di(C_{1-6})alkylaminomethyl, C_{2-6} alkylcarbonylamino, arylcarbonylamino, C_{2-6} alkoxycarbonylamino, *N*-(C_{1-6})alkyl-*N*-(C_{2-6})alkoxycarbonylamino, C_{1-6} alkylsulphonylamino, arylsulphonylamino, C_{1-6} alkylsulphonylaminomethyl, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, di(C_{1-6})alkylaminocarbonylamino, mono- or diarylaminocarbonylamino, pyrrolidinylcarbonylamino, piperidinylcarbonylamino, aminocarbonyl, C_{1-6} alkylaminocarbonyl, di(C_{1-6})alkylaminocarbonyl, aminosulphonyl, C_{1-6} alkylaminosulphonyl, di(C_{1-6})alkylaminosulphonyl, aminosulphonylmethyl, C_{1-6} alkylaminosulphonylmethyl and di(C_{1-6})alkylaminosulphonylmethyl.

A particular substituent on the group R^1 is methyl.

As used herein, the expression "C_{1-6} alkyl" includes methyl and ethyl groups, and straight-chained or branched propyl, butyl, pentyl and hexyl groups. Particular alkyl groups are methyl, ethyl, *n*-propyl,

isopropyl and *tert*-butyl. Derived expressions such as "C_{1-6} alkoxy", "C_{1-6} alkylthio" and "C_{1-6} alkylamino" are to be construed accordingly.

Typical aryl groups include phenyl and naphthyl, preferably phenyl.

The expression "aryl(C_{1-6})alkyl" as used herein includes benzyl, phenylethyl, phenylpropyl and naphthylmethyl, especially phenylethyl.

Suitable heteroaryl groups include pyridinyl, quinolinyl, isoquinolinyl, pyridazinyl, pyrimidinyl, pyrazinyl, quinoxalinyl, furyl, benzofuryl, dibenzofuryl, thienyl, benzthienyl, pyrrolyl, indolyl, pyrazolyl, indazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, benzimidazolyl, oxadiazolyl, thiadiazolyl, triazolyl and tetrazolyl groups.

The expression "heteroaryl(C_{1-6})alkyl" as used herein includes furylmethyl, furylethyl, thienylmethyl, thienylethyl, pyrazolylmethyl, pyrazolylethyl, oxazolylmethyl, oxazolylethyl, isoxazolylmethyl, thiazolylmethyl, thiazolylethyl, imidazolylmethyl, imidazolylethyl, benzimidazolylmethyl, oxadiazolylmethyl, oxadiazolylethyl, thiadiazolylmethyl, thiadiazolylethyl, triazolylmethyl, triazolylethyl, tetrazolylmethyl, tetrazolylethyl, pyridinylmethyl, pyridinylethyl, pyridazinylmethyl, pyrimidinylmethyl, pyrazinylmethyl, quinolinylmethyl, isoquinolinylmethyl and quinoxalinylmethyl.

Typical heterocycloalkyl groups include azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl and imidazolidinonyl groups.

A particular C_{3-7} heterocycloalkyl(C_{1-6})alkyl group is imidazolidinonylethyl.

The term "halogen" as used herein includes fluorine, chlorine, bromine and iodine, especially fluorine or chlorine.

For use in medicine, the salts of the compounds of formula I will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which

may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, methanesulphonic acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, oxalic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g. sodium or potassium salts; alkaline earth metal salts, e.g. calcium or magnesium salts; and salts formed with suitable organic ligands, e.g. quaternary ammonium salts.

Where the compounds according to the invention have at least one asymmetric centre, they may accordingly exist as enantiomers. Where the compounds according to the invention possess two or more asymmetric centres, they may additionally exist as diastereoisomers. In addition, where the broken line is absent from formula I as depicted above, the resulting compounds can, by virtue of the azabicyclic ring system, exist as discrete *endo* and *exo* stereoisomers. Moreover, where the broken line in formula I represents a chemical bond, the resulting compounds can, by virtue of the azabicyclic ring system, exist as discrete enantiomers. It is to be understood that all possible stereoisomers of the compounds according to the invention, and mixtures thereof in any proportion, are encompassed within the scope of the present invention.

Suitably, A and B independently represent hydrogen, fluoro, chloro, cyano, nitro, trifluoromethyl, trifluoromethoxy, methyl or methoxy; or A and B, when attached to adjacent carbon atoms, together represent methylenedioxy.

Particular values for the substituent A in the compounds of formula I above include hydrogen, fluoro, trifluoromethyl, methyl and methoxy, especially hydrogen or fluoro.

Suitably, B represents hydrogen, fluoro, chloro, cyano, nitro, trifluoromethyl, trifluoromethoxy, methyl or methoxy, especially hydrogen.

Particular values for the substituent X include hydrogen, fluoro and methoxy, especially hydrogen.

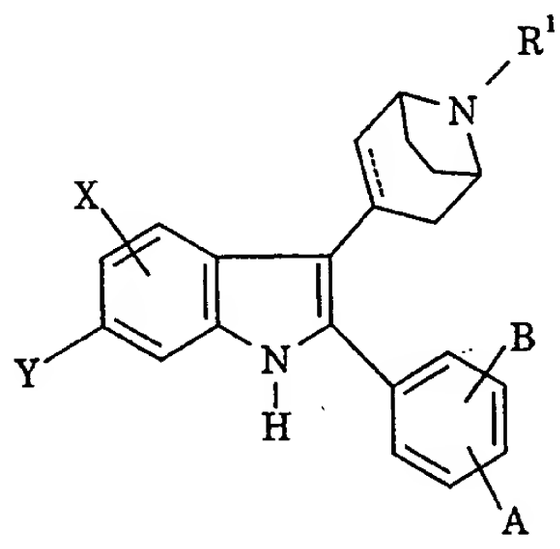
Suitably, Y represents hydrogen, fluoro, chloro, bromo, methyl, methoxy or phenyl, especially hydrogen or fluoro.

In one embodiment, the moiety Q represents $-CH_2CH_2-$. In another embodiment, Q represents $-CH_2CH_2CH_2-$. Suitably, Q represents $-CH_2CH_2-$.

Suitably, R^1 represents hydrogen, methyl, benzyl, phenylethyl, thienylethyl, methyl-pyrazolylethyl or imidazolidinonylethyl. In one embodiment, R^1 represents hydrogen.

Suitably, R^2 represents hydrogen or hydroxy, especially hydrogen.

A particular sub-class of compounds according to the invention is represented by the compounds of formula II, and salts thereof:



(II)

wherein

A, B, X, Y, R^1 and the broken line are as defined with reference to formula I above.

Specific compounds within the scope of the present invention include:

3-[8-(2-phenylethyl)-8-azabicyclo[3.2.1]oct-2-en-3-yl]-2-phenyl-1*H*-indole;

endo-3-[8-(2-phenylethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-phenyl-1*H*-indole;

endo-3-(8-azabicyclo[3.2.1]oct-3-yl)-2-phenyl-1*H*-indole;

3-(8-azabicyclo[3.2.1]oct-2-en-3-yl)-2-phenyl-1*H*-indole;

3-(8-methyl-8-azabicyclo[3.2.1]oct-2-en-3-yl)-2-phenyl-1*H*-indole;

3-(8-azabicyclo[3.2.1]oct-2-en-3-yl)-6-fluoro-2-phenyl-1*H*-indole;

3-(8-azabicyclo[3.2.1]oct-2-en-3-yl)-6-fluoro-2-(3-fluorophenyl)-1*H*-indole;

3-(8-azabicyclo[3.2.1]oct-2-en-3-yl)-6-fluoro-2-(4-fluorophenyl)-1*H*-indole;

3-(8-azabicyclo[3.2.1]oct-2-en-3-yl)-2-(4-fluorophenyl)-1*H*-indole;

3-(8-azabicyclo[3.2.1]oct-2-en-3-yl)-2-(benzo[1,3]dioxol-5-yl)-1*H*-indole;

9-methyl-3-(2-phenyl-1*H*-indol-3-yl)-9-azabicyclo[3.3.1]non-2-ene;

endo-3-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2-phenyl-1*H*-indole;

exo-3-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2-phenyl-1*H*-indole;

endo-3-(8-azabicyclo[3.2.1]oct-3-yl)-2-(4-fluorophenyl)-1*H*-indole;

endo-3-(8-azabicyclo[3.2.1]oct-3-yl)-2-(benzo[1,3]dioxol-5-yl)-1*H*-indole;

endo-3-(8-azabicyclo[3.2.1]oct-3-yl)-6-fluoro-2-(4-fluorophenyl)-1*H*-indole;

endo-2-phenyl-3-[8-(2-(thien-3-yl)ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1*H*-indole;

endo-3-[8-(2-(1-methyl-1*H*-pyrazol-4-yl)ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-phenyl-1*H*-indole;

1-[2-(3-(2-phenyl-1*H*-indol-3-yl)-8-azabicyclo[3.2.1]oct-2-en-8-yl)ethyl]-imidazolidin-2-one;

3-(8-aza-2-hydroxybicyclo[3.2.1]oct-3-yl)-2-phenyl-1*H*-indole;

and salts thereof.

The invention also provides pharmaceutical compositions comprising one or more of the compounds according to this invention in association with a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, auto-injector devices or suppositories; for oral, parenteral, intranasal, sublingual or rectal

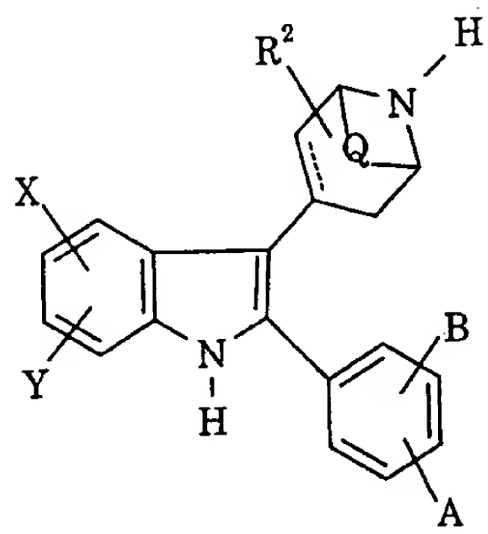
administration, or for administration by inhalation or insufflation. Alternatively, the compositions may be presented in a form suitable for once-weekly or once-monthly administration; for example, an insoluble salt of the active compound, such as the decanoate salt, may be adapted to provide a depot preparation for intramuscular injection. An erodible polymer containing the active ingredient may be envisaged. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. Favoured unit dosage forms contain from 1 to 100 mg, for example 1, 2, 5, 10, 25, 50 or 100 mg, of the active ingredient. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

In the treatment of schizophrenia, a suitable dosage level is about 0.01 to 250 mg/kg per day, preferably about 0.05 to 100 mg/kg per day, and especially about 0.05 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day.

If desired, the compounds according to this invention may be co-administered with another anti-schizophrenic medicament, for example one producing its effects *via* dopamine D_2 and/or D_4 receptor subtype blockade. In such circumstances, an enhanced anti-schizophrenic effect may be envisaged without a corresponding increase in side-effects such as those caused by, for example, D_2 receptor subtype blockade; or a comparable anti-schizophrenic effect with reduced side-effects may alternatively be envisaged. Such co-administration may be desirable where a patient is already established on an anti-schizophrenic treatment regime involving conventional anti-schizophrenic medicaments. Suitable anti-schizophrenic medicaments of use in combination with the compounds according to the present invention include haloperidol, chlorpromazine, mesoridazine, thioridazine, acetophenazine, fluphenazine, perphenazine, trifluoperazine, chloroprothixene, thiothixene, clozapine, olanzapine, pimozide, molindone, loxapine, sulpiride, risperidone, xanomeline, fananserin and ziprasidone, and pharmaceutically acceptable salts thereof.

The compounds according to the present invention wherein R^1 is other than hydrogen may be prepared by a process which comprises attachment of the R^1 moiety to a compound of formula III:



(III)

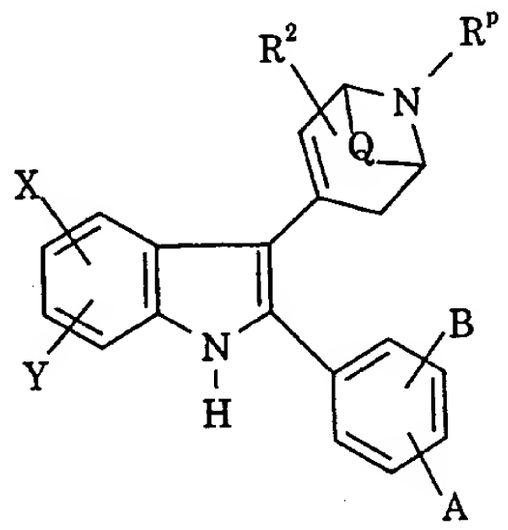
wherein A, B, X, Y, Q, R^2 and the broken line are as defined above; by conventional means including N-alkylation.

Attachment of the R^1 moiety to the compounds of formula III may conveniently be effected by standard alkylation techniques. One example thereof comprises treatment with an alkyl halide such as methyl iodide, an aryl(C_{1-6})alkyl halide such as benzyl bromide or 2-phenylethyl bromide, or a C_{3-7} heterocycloalkyl(C_{1-6})alkyl halide such as 2-(imidazolidin-2-on-1-yl)ethyl chloride, typically under basic conditions, e.g. potassium carbonate or caesium carbonate in isopropanol or *N,N*-dimethylformamide, optionally in the presence of sodium iodide. Another example comprises treatment of the compound of formula III with an aryl(C_{1-6})alkyl mesylate such as 2-phenylethyl methanesulphonate, or a heteroaryl(C_{1-6})alkyl mesylate such as 1-methyl-4-(2-methanesulphonyloxyethyl)pyrazole, typically under basic conditions, e.g. postassium carbonate or sodium carbonate in *N,N*-dimethylformamide or 1,2-dimethoxyethane, optionally in the presence of sodium iodide.

Alternatively, the R^1 moiety may conveniently be attached by reductive alkylation, which may be accomplished in a single step, or as a

two-step procedure. The single-step approach suitably comprises treating the required compound of formula III as defined above with the appropriate aldehyde, e.g. formaldehyde, benzaldehyde or phenylacetaldehyde, in the presence of a reducing agent such as sodium cyanoborohydride. In a typical two-step procedure, for the preparation of a compound of formula I wherein R^1 corresponds to a group of formula $-CH_2R^{1a}$, a carboxylic acid derivative of formula R^{1a}-CO_2H is condensed with the required compound of formula III, suitably in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 1-hydroxybenzotriazole hydrate, to afford a compound corresponding to formula I wherein R^1 represents $-COR^{1a}$; the carbonyl group thereof can then be reduced, for example by treatment with diisobutylaluminium hydride, or with borane-tetrahydrofuran complex followed by treatment with a mineral acid such as methanolic hydrochloric acid, and the required compound of formula I thereby obtained.

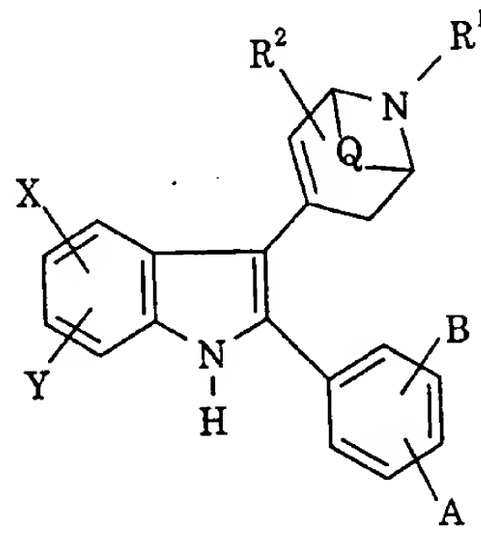
The compounds of formula III above wherein the broken line is absent may be prepared by reduction of the corresponding compound of formula IV:



(IV)

wherein A, B, X, Y, Q and R^2 are as defined above, and R^p represents an amino-protecting group; followed by removal of the amino-protecting group R^p.

Similarly, the compounds according to the invention wherein the broken line is absent may be prepared by a process which comprises reducing a compound of formula V:



(V)

wherein A, B, X, Y, Q, R^1 and R^2 are as defined above.

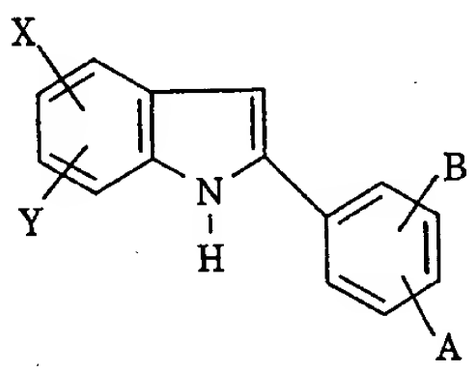
Reduction of the compounds of formula IV or V may conveniently be accomplished by conventional catalytic hydrogenation, which comprises treating the appropriate compound with hydrogen in the presence of a hydrogenation catalyst such as palladium on charcoal. Alternatively, compound IV or V may be reduced by transfer hydrogenation using a hydrogenation catalyst such as palladium on charcoal in the presence of a hydrogen donor such as ammonium formate, typically in a lower alkanol solvent such as methanol. In another alternative, compound IV or V may be reduced by treatment with triethylsilane, typically in the presence of trifluoroacetic acid.

The amino-protecting group R^P in the compounds of formula IV is suitably benzyl, in which case the amino-protecting group R^P can conveniently be removed as necessary by transfer hydrogenation utilising the conditions described above. Alternatively, the amino-protecting group R^P may be a carbamoyl moiety such as benzyloxycarbonyl, which can conveniently be removed as necessary by treatment with hydrogen in the

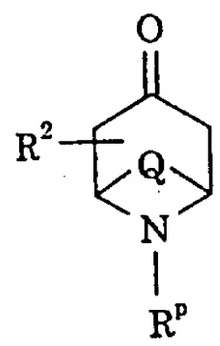
presence of a hydrogenation catalyst such as palladium on charcoal, typically in methanol/formic acid.

Under certain circumstances, for example where R^1 in the compounds of formula V represents 2-phenylethyl, reduction under transfer hydrogenation conditions may partially remove the R^1 substituent, giving rise to a mixture of products containing the desired compound of formula I and the corresponding compound of formula I wherein R^1 is hydrogen. These compounds may be conveniently separated by conventional techniques including chromatography.

The intermediates of formula IV above may be prepared by reacting a compound of formula VI with the appropriate compound of formula VII:



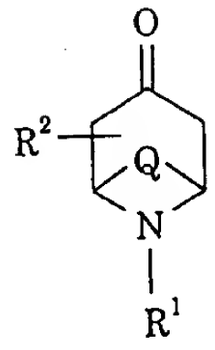
(VI)



(VII)

wherein A, B, X, Y, Q, R^2 and R^P are as defined above.

Similarly, the compounds according to the invention wherein the broken line represents a chemical bond, corresponding to the compounds of formula V above, may be prepared by a process which comprises reacting a compound of formula VI as defined above with the appropriate compound of formula VIII:

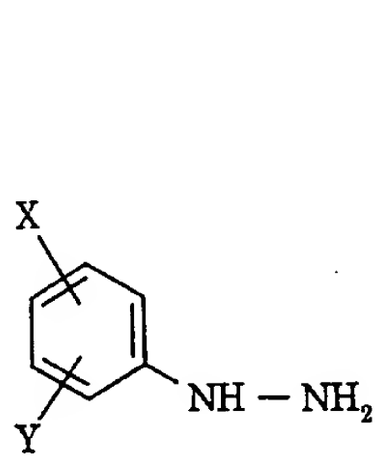


(VIII)

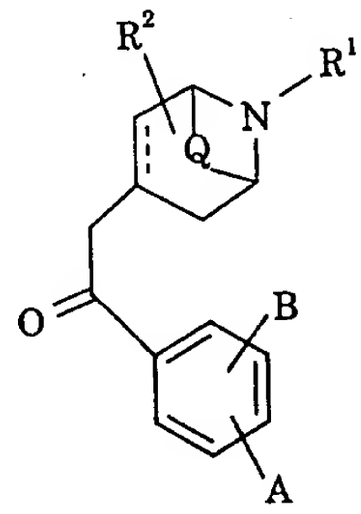
wherein Q, R^1 and R^2 are as defined above.

The reaction between compound VI and compound VII or VIII is conveniently effected by heating the reactants under acidic conditions, typically in a mixture of phosphoric acid and acetic acid at an elevated temperature.

In another procedure, the compounds according to the invention may be prepared by a process which comprises reacting a compound of formula IX or an acid addition salt thereof, typically the hydrochloride salt, with a compound of formula X:



(IX)

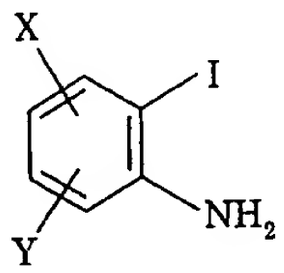


(X)

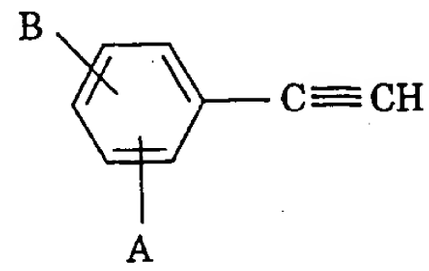
wherein A, B, X, Y, Q, R^1, R^2 and the broken line are as defined above.

The reaction between compounds IX and X, which is an example of the well-known Fischer indole synthesis, is suitably effected by stirring in ethanol at 25°C, followed by heating in trifluoroacetic acid at 70°C.

The intermediates of formula VI above may be prepared by reacting a compound of formula XI with a compound of formula XII (cf. Larock and Yum, *J. Am. Chem. Soc.*, 1991, **113**, 6689):



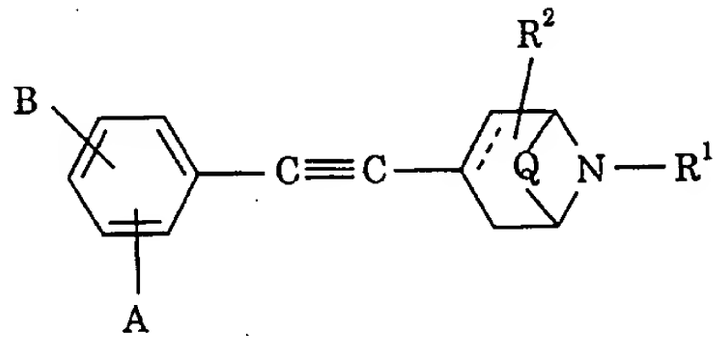
(XI)



(XII)

wherein A, B, X and Y are as defined above; in the presence of a transition metal catalyst.

Similarly, the compounds according to the invention may be prepared by a process which comprises reacting a compound of formula XI as defined above with a compound of formula XIII:

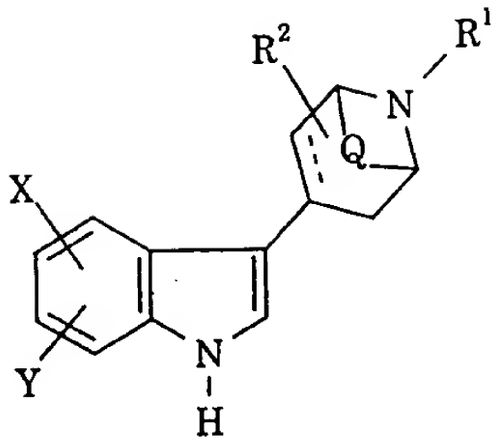


(XIII)

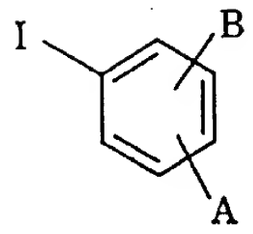
wherein A, B, Q, R^1, R^2 and the broken line are as defined above; in the presence of a transition metal catalyst.

The transition metal catalyst employed in the reaction between compound XI and compound XII or XIII is suitably a palladium-containing catalyst, preferably dichlorobis(triphenylphosphine)palladium(II), in which case the reaction is advantageously effected in the presence of copper(I) iodide.

In a further procedure, the compounds according to the invention may be prepared by a process which comprises reacting a compound of formula XIV with a compound of formula XV:



(XIV)



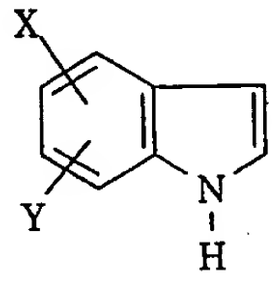
(XV)

wherein A, B, X, Y, Q, R^1, R^2 and the broken line are as defined above; in the presence of a transition metal catalyst.

The transition metal catalyst employed in the reaction between compounds XIV and XV is suitably a palladium-containing catalyst, preferably tetrakis(triphenylphosphine)palladium(0), in which case the reaction is conveniently effected in the presence of zinc chloride and the base obtained from the reaction between 2,2,6,6-tetramethylpiperidine and a lower alkyllithium, e.g. *n*-butyllithium.

The intermediates of formula XIV wherein the broken line is absent may be prepared by reducing the corresponding compound XIV wherein the broken line represents a chemical bond, under conditions analogous to those described above for reduction of the compounds of formula V above.

The intermediates of formula XIV wherein the broken line represents a chemical bond may be prepared by reacting a compound of formula VIII as defined above with a compound of formula XVI:



(XVI)

wherein X and Y are as defined above; under conditions analogous to those described above for the reaction between compounds VI and VIII.

Where they are not commercially available, the starting materials of formula VII, VIII, IX, X, XI, XII, XIII, XV and XVI may be prepared by procedures analogous to those described in the accompanying Examples, or by standard methods well known from the art.

It will be appreciated that any compound of formula I initially obtained from any of the above processes may, where appropriate, subsequently be elaborated into a further desired compound of formula I using techniques known from the art. Indeed, as will be appreciated, the compounds of formula III and V above, and the compounds of formula IV wherein the amino-protecting group R^p is, for example, benzyl, are compounds according to the invention in their own right. By way of example, a compound of formula I initially obtained wherein the broken line represents a chemical bond and R^2 is hydrogen may be converted into the corresponding compound, wherein the broken line is absent and R^2 represents hydroxy at the 2-position of the azabicyclic ring system, by hydroboration followed by oxidation.

Where the above-described processes for the preparation of the compounds of use in the invention give rise to mixtures of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography. The compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The compounds may, for example, be resolved into their component enantiomers by standard techniques such as preparative HPLC, or the formation of diastereomeric pairs by salt formation with an optically active acid, such as (-)-di-*p*-toluoyl-d-tartaric acid and/or (+)-di-*p*-toluoyl-l-tartaric acid, followed by fractional crystallization and regeneration of the free base. The compounds may also be resolved by formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry*, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The following Examples illustrate the preparation of compounds of use in the invention.

The compounds in accordance with this invention potently inhibit [^{3}H]-ketanserin binding to the human 5-HT_{2A} receptor expressed in clonal cell lines. Moreover, those compounds of the invention which have been tested display a selective affinity for the 5-HT_{2A} receptor relative to the dopamine D_2 receptor.

The compounds of the accompanying Examples were all found to possess a K_i value for displacement of [^{3}H]-ketanserin from the human 5-HT_{2A} receptor, when expressed in Chinese hamster ovary (CHO) clonal cell lines, of 100 nM or less.

EXAMPLE 1

3-[8-(2-Phenylethyl)-8-azabicyclo[3.2.1]oct-2-en-3-yl]-2-phenyl-1*H*-indole

2-Phenylindole (5 g, 25.9 mmol) and 8-(2-phenylethyl)-8-azabicyclo[3.2.1]octan-3-one (10 g, 43.6 mmol) were heated in acetic acid (50 ml) and 1M phosphoric acid (25 ml) at 80°C for 5 days. The mixture was cooled, poured into a mixture of ice and aqueous ammonia, and extracted with ethyl acetate (x3). The combined organic layers were washed with water and brine, dried, evaporated *in vacuo*, and purified by flash chromatography, eluting with dichloromethane:methanol:880 ammonia (90:10:1 v/v), then again with dichloromethane:methanol:880

ammonia (97:3:0.3 v/v), to give the title compound (2.1 g, 20%) as a dark glass. A portion was recrystallised from EtOH/MeOH to give tan crystals, mp > 300°C (Found: C, 77.65; H, 6.51; N, 6.05. $C_{29}H_{28}N_2$ with 10% ash requires C, 77.50; H, 6.28; N, 6.23%); δ_H (360 MHz, $CDCl_3$) 1.70 (1H, d, *J* 18, tropane H-4), 1.70-1.76 (1H, m, aliphatic H), 1.95-2.2 (3H, m, aliphatic H), 2.59 (1H, d with other fine coupling, *J* 18, tropane H-4'), 2.80-3.10 (4H, m, aliphatic H), 3.41 (1H, t with other fine coupling, *J* 5, tropane H-1 or tropane H-5), 3.58 (1H, t, *J* 5, tropane H-5 or tropane H-1), 6.00 (1H, d, *J* 5, tropane H-2), 7.10-7.40 (12H, m, ArH), 7.57 (1H, dd, *J* 1 and 8, ArH), 7.62 (1H, d, *J* 8, ArH), 8.20 (1H, br s, NH); *m/z* (ES^+) 405 (M^++H).

EXAMPLE 2

endo-3-[8-(2-Phenylethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-phenyl-1*H*-indole and *endo*-3-(8-Azabicyclo[3.2.1]oct-3-yl)-2-phenyl-1*H*-indole

3-[8-(2-Phenylethyl)-8-azabicyclo[3.2.1]oct-2-en-3-yl]-2-phenyl-1*H*-indole (300 mg, 0.74 mmol), ammonium formate (1 g, 12.6 mmol) and palladium on carbon (10% w/w, 150 mg) were refluxed in MeOH (20 ml) for 2 h. Ammonium formate (1 g, 12.6 mmol) was added and the mixture refluxed for 24 h. It was then filtered, ammonium formate (1 g, 12.6 mmol) and palladium on carbon (10% w/w, 150 mg) added and refluxed for 24 h. Ammonium formate (1 g, 12.6 mmol) was added and the mixture refluxed for a further 24 h. The mixture was cooled, filtered, evaporated and purified by preparative thin layer chromatography, eluting with dichloromethane:methanol:880 ammonia (90:10:1 v/v), then again with dichloromethane:methanol:880 ammonia (95:5:0.5 v/v), to give *endo*-3-[8-(2-phenylethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-phenyl-1*H*-indole (85 mg, 21%) as white needles, mp 123-124°C (from EtOAc); and *endo*-3-(8-azabicyclo[3.2.1]oct-3-yl)-2-phenyl-1*H*-indole (37 mg, 14%) as white crystals, mp 186-190°C (from EtOAc).

endo-3-[8-(2-Phenylethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-phenyl-1*H*-indole: δ_H (400 MHz, $CDCl_3$) 1.70-1.80 (2H, m, tropane H-6, *syn* to indole), 1.91 (2H, t, *J* 13, tropane H-2, *cis* to indole), 2.10-2.20 (2H, m, tropane H-6, *anti* to indole), 2.30-2.50 (2H, m, tropane H-2, *trans* to indole), 2.53 (2H, t, *J* 8, $PhCH_2$), 2.79 (2H, t, *J* 8, NCH_2), 3.35-3.45 (2H, m, tropane H-1), 3.50-3.60 (1H, m, tropane H-3), 7.10-7.50 (13H, m, ArH), 7.71 (1H, d, *J* 8, indole H-4), 7.90 (1H, br s, NH). In a NOESY experiment, cross peaks were observed between the signals at 3.50-3.60 and 2.30-2.50, and between the signals at 2.10-2.20 and 1.91; this shows the stereochemistry of the compound. *m/z* (ES^+) 407 (M^++H).

endo-3-(8-Azabicyclo[3.2.1]oct-3-yl)-2-phenyl-1*H*-indole: (Found: C, 82.40; H, 7.34; N, 9.03. $C_{21}H_{22}N_2 \cdot 0.25\ H_2O$ requires C; 82.18; H, 7.39; N, 9.13%); δ_H (360 MHz, $CDCl_3$) 1.80-2.00 (6H, m, tropane H), 2.20-2.30 (2H, m, tropane H-2, *trans* to indole), 3.20-3.30 (1H, m, tropane H-3), 3.50-3.60 (2H, m, tropane H-1), 7.10 (1H, t, *J* 8, indole H), 7.17 (1H, t, *J*, indole H), 7.30-7.50 (6H, m, ArH), 7.72 (1H, d, *J* 8, indole H-4). Irradiation of the signal at 3.20-3.30 gave positive nOe's to a signal at 7.40 and the signal at 2.20-2.30; also irradiation of the signal at 7.72 gave positive nOe's to two of the signals in the multiplet 1.80-2.00. Since one of these must be tropane H-6, this shows the stereochemistry to be *endo*. *m/z* (ES^+) 303 (M^++H).

EXAMPLE 3

3-(8-Azabicyclo[3.2.1]oct-2-en-3-yl)-2-phenyl-1*H*-indole

2-Phenylindole (5 g, 25.9 mmol) and 8-azabicyclo[3.2.1]octan-3-one hydrochloride (9.3 g, 57 mmol) were heated in acetic acid (50 ml) and 1M phosphoric acid (25 ml) at 80°C for 4 days. The mixture was cooled, water (200 ml) added, and the solid product collected by filtration, washed with water and ether and dried to give a grey powder (presumably the phosphate salt, 8 g, 77%). The mother liquors were poured into ice/

ammonia, and more solid collected, washed with water, and recrystallised from aqueous MeOH to give tan crystals (0.63 g, a further 8%), mp 254-255°C; (Found: C, 81.55; H, 6.77; N, 9.06. $C_{21}H_{20}N_2 \cdot 0.5\ H_2O$ requires C; 81.52; H, 6.84; N, 9.05%); δ_H (360 MHz, $CDCl_3$) 1.70-1.90 (2H, m, aliphatic H), 1.77 (1H, d, *J* 17, tropane H-4), 1.90-2.00 (2H, m, aliphatic H), 2.57 (1H, d with other fine coupling, *J* 17, tropane H-4'), 3.55 (1H, t with other fine coupling, *J* 5, tropane H-1 or tropane H-5), 3.63 (1H, t, *J* 5, tropane H-5 or tropane H-1), 5.99 (1H, d, *J* 5, tropane H-2), 6.99 (1H, t, *J* 7, indole-H), 7.09 (1H, t, *J* 7 indole-H), 7.30-7.40 (2H, m, ArH), 7.40-7.50 (3H, m, ArH), 7.67 (2H, d, *J* 8, ArH), 11.20 (1H, br s, NH); *m/z* (ES^+) 301 (M^++H).

EXAMPLE 4

3-(8-Methyl-8-azabicyclo[3.2.1]oct-2-en-3-yl)-2-phenyl-1*H*-indole

Oxalate salt, colourless plates, mp 249-250°C (from ethanol) (Found: C, 68.75; H, 6.04; N, 6.42. $C_{22}H_{22}N_2.C_2H_2O_4.0.8\ H_2O$ requires C, 68.82; H, 6.16; N, 6.69%); δ_H (360 MHz, d_6-DMSO) 2.00-2.10 (1H, m, aliphatic H), 2.14 (1H, d with other fine coupling, *J* 18, tropane H-4'), 2.20-2.40 (3H, m, aliphatic H), 2.80 (3H, s, CH_3), 2.90-3.00 (1H, m, aliphatic H), 3.90-4.00 (1H, m, tropane H-1 or tropane H-5), 4.10-4.20 (1H, m, tropane H-5 or tropane H-1), 6.00 (1H, d, *J* 5, tropane H-2), 7.05 (1H, t, *J* 7, ArH), 7.15 (1H, t, *J* 7, ArH), 7.40-7.50 (2H, m, ArH), 7.52 (1H, t, *J* 7, ArH), 7.60-7.70 (3H, m, ArH), 11.50 (1H, br s, NH); *m/z* (ES^+) 315 (M^++H).

EXAMPLE 5

3-(8-Azabicyclo[3.2.1]oct-2-en-3-yl)-6-fluoro-2-phenyl-1*H*-indole

5-Fluoro-2-iodoaniline (7.50 g, 0.031 mol) and phenylacetylene (6.46 g, 0.062 mol) were dissolved in butylamine (100 ml) and the mixture purged with nitrogen for 15 min. Dichlorobis(triphenylphosphine)-palladium(II) (0.50 g) and copper(I) iodide (0.10 g) were added and the

reaction mixture heated at reflux for 18 h. The solvent was removed *in vacuo* and the residue purified by flash column chromatography on silica eluting with ethyl acetate/hexane (95:5) to give 1-(2-amino-4-fluorophenyl)-2-phenylacetylene (5.5 g, 84%) as a yellow solid. The solid was dissolved in DMF (35 ml), copper(I) iodide (2.36 g) and calcium carbonate (2.48 g) added and the mixture heated at 120°C for 24 h. The solvent was removed, the residue dissolved in ethyl acetate and washed with saturated ammonium chloride solution, water and brine, dried over sodium sulphate and evaporated to yield 2-phenyl-6-fluoro-1*H*-indole (5.4 g, 98%). This was then coupled to 8-azabicyclo[3.2.1]octan-3-one hydrochloride to give the title product as a cream solid, mp 236-238°C; (Found C, 76.40; H, 6.17; N, 8.45. $C_{21}H_{19}FN_2 \cdot 0.5\ H_2O$ requires C, 76.62; H, 6.18; N, 8.51%); δ_H (360 MHz, $CDCl_3$) 1.80-2.20 (5H, m, tropane H), 2.50-2.60 (1H, m, tropane H-4), 2.60-2.70 (1H, m, tropane H-4), 3.70-3.80 (1H, m, tropane H-1 or H-5), 3.80-3.90 (1H, m, tropane H-1 or H-5), 6.10 (1H, d, *J* 5.3, tropane H-2), 6.90 (1H, dt, *J* 2.2 and 9.2, indole H-5), 7.05 (1H, dd, *J* 2.2 and 9.2, indole H-7), 7.30-7.40 (1H, m, ArH), 7.40-7.50 (2H, m, ArH), 7.50-7.60 (4H, m, ArH), 8.30 (1H, s, indole NH); *m/z* (ES^+) 319 (M^++H).

EXAMPLE 6

3-(8-Azabicyclo[3.2.1]oct-2-en-3-yl)-6-fluoro-2-(3-fluorophenyl)-1*H*-indole

mp 205-208°C; (Found C, 58.29; H, 6.04; N, 6.59. $C_{21}H_{19}FN_2 \cdot HCl \cdot 3.2\ H_2O$ requires C, 58.59; H, 5.95; N, 6.51%); δ_H (360 MHz, d_6-DMSO) 1.60-1.90 (2H, m, tropane H), 1.90-2.10 (2H, m, tropane H), 2.40-2.60 (2H, m, tropane H), 3.60-3.70 (2H, m, tropane H-1 and H-5), 6.00 (1H, d, *J* 5.3, tropane H-2), 6.80-6.90 (1H, m, ArH), 7.10-7.20 (2H, m, ArH), 7.40-7.60 (4H, m, ArH), 11.50 (1H, s, indole NH); *m/z* (ES^+) 337 (M^++H).

EXAMPLE 7

3-(8-Azabicyclo[3.2.1]oct-2-en-3-yl)-6-fluoro-2-(4-fluorophenyl)-1*H*-indole

Tan crystals, mp 274-276°C (from EtOAc); (Found: C, 70.65; H, 5.42; N, 8.14. $C_{21}H_{18}F_2N_2 \cdot 1.1H_2O$ requires C, 70.81; H, 5.72; N, 7.86%); δ_H (360 MHz, d_6-DMSO) 1.80-1.90 (2H, m, CH_2), 1.78 (1H, d, *J* 16, tropane H-4), 1.90-2.10 (2H, m, CH_2), 2.60 (1H, d, *J* 16, tropane H-4'), 3.55-3.60 (1H, m, tropane H-1 or tropane H-5), 3.60-3.65 (1H, m, tropane H-5 or tropane H-1), 6.00 (1H, d, *J* 5, tropane H-2), 6.87 (1H, dt, *J* 2 and 9, indole H-5), 7.09 (1H, dd, *J* 2 and 10, indole H-7), 7.31 (2H, t, *J* 9, ArH *o* to F), 7.48 (1H, dd, *J* 5.5 and 9, indole H-4), 7.66 (2H, dd, *J* 5.5 and 9, ArH *m* to F), 11.5 (1H, br s, NH); *m/z* (ES^+) 337 (M^++H).

EXAMPLE 8

3-(8-Azabicyclo[3.2.1]oct-2-en-3-yl)-2-(4-fluorophenyl)-1*H*-indole

8-Azabicyclo[3.2.1]octan-3-one hydrochloride (11.6 g, 85.6 mmol) was added to a solution of indole (5.0 g, 42.7 mmol) in glacial acetic acid (50 ml) and 1M phosphoric acid (15 ml) and the mixture heated at 100°C for 16 hours. The cooled reaction was poured into ice/ammonia (100 ml) and extracted with ethyl acetate (3 x 100 ml). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was taken into dichloromethane (100 ml), *N,N*-dimethylaminopyridine (5 g, 41.5 mmol) and di-*tert*-butyldicarbonate (10 g, 46.0 mmol) added, and the reaction stirred at room temperature for 3 hours. The reaction mixture was washed with saturated sodium hydrogen carbonate solution (100 ml), water (100 ml), citric acid (10% w/v, 100 ml), water (100 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography eluting with dichloromethane:methanol (98:2 w/v) to give 3-(8-*tert*-butoxycarbonyl-8-azabicyclo[3.2.1]oct-2-en-3-yl)-1*H*-indole-1-carboxylic acid *tert*-butyl ester, as a cream foam (7 g, 39%); δ_H (250 MHz,

$CDCl_3$) 1.40 (9H, s, *t*-BuH), 1.60 (9H, s, *t*-BuH), 1.90-2.00 (2H, m, tropane H-7), 2.10-2.30 (2H, m, tropane H-6), 3.00-3.20 (2H, m, tropane H-4), 4.30-4.60 (2H, m, tropane H-1 and H-5), 6.60 (1H, d, *J* 5, tropane H-2), 7.20-7.40 (2H, m, indole H-5 and H-6), 7.50 (1H, s, indole H-2), 7.80 (1H, d, *J* 7.3, indole H-7), 8.10 (1H, d, *J* 7.7, indole H-4). 1.6 M *n*-Butyllithium (4.4 ml, 7.0 mmol) was added to a solution of 2,2,6,6-tetramethylpiperidine (1.2 ml, 7.1 mmol) in THF (10 ml) at 0°C and the mixture stirred for 15 minutes. The reaction was cooled to -78°C before addition of 3-(8-*tert*-butoxycarbonyl-8-azabicyclo[3.2.1]oct-2-en-3-yl)-1*H*-indole-1-carboxylic acid *tert*-butyl ester (1.0 g, 2.35 mmol) in THF (10 ml) and stirring was continued for 3 hours. 0.5 M Zinc chloride (9 ml, 4.5 mmol) in THF was added and the reaction stirred for 30 minutes at -78°C, then allowed to warm to room temperature over a further 30 minutes before the addition of 4-fluoroiodobenzene (0.6 ml, 5.2 mmol) and tetrakis-(triphenylphosphine)palladium(0) (200 mg, 0.17 mmol). The reaction was heated at reflux under nitrogen for 19 hours, poured into water (60 ml) and extracted with ethyl acetate (2 x 100 ml). The combined organics were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was taken into dichloromethane (10 ml), trifluoroacetic acid (5 ml) added and the mixture stirred for 2 hours, washed with water (20 ml), saturated sodium hydrogen carbonate solution (20 ml), water (20 ml), dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography eluting with dichloromethane:methanol (90:10 w/v) to give the *title compound* as a white foam (300 mg, 40%); mp 143-145°C; δ_H (400 MHz, d_6-DMSO) 1.90-2.00 (1H, m, tropane H), 2.00-2.30 (4H, m, tropane H), 2.80-2.90 (1H, m, tropane H), 3.10-3.20 (1H, m, tropane H), 4.10-4.20 (1H, m, tropane H-5 or H-1), 4.30-4.40 (1H, m, tropane H-1 or H-5), 5.90 (1H, d, *J* 8, tropane H-2), 7.05-7.10 (1H, m, indole H), 7.15-7.20 (1H, m, indole H), 7.30-7.40 (3H, m, ArH), 7.60-7.70 (3H, m, ArH), 8.90 (1H, br s, indole NH); *m/z* (ES^+) 319 (M^++H).

EXAMPLE 9

3-(8-Azabicyclo[3.2.1]oct-2-en-3-yl)-2-(benzo[1,3]dioxol-5-yl)-1*H*-indole

Oxalate salt, white crystals, mp 139-141°C; (Found C, 62.72; H, 5.47; N, 5.70. $C_{22}H_{20}N_2O_2 \cdot C_2H_2O_4 \cdot 1.5\ H_2O$ requires C, 62.47; H, 5.46; N, 6.07%); δ_H (360 MHz, $CDCl_3$) 1.60-1.70 (2H, m, tropane H), 1.80-1.90 (1H, m, tropane H), 2.20-2.40 (3H, m, tropane H), 2.90-3.00 (1H, m, tropane H), 3.90-4.00 (1H, m, tropane H-1 or H-5), 4.10-4.15 (1H, m, tropane H-5 or H-1), 6.00 (2H, s, methylenedioxy H), 6.10 (1H, d, *J* 5.4, tropane H-2), 6.90 (1H, d, *J* 7.5, indole H-5), 7.00-7.10 (2H, m, ArH), 7.10-7.20 (2H, m, indole H and ArH), 7.40 (1H, d, *J* 7.2, indole H-7), 7.65 (1H, d, *J* 7.2, indole H-4), 8.20 (1H, br s, indole NH).

EXAMPLE 10

9-Methyl-3-(2-phenyl-1*H*-indol-3-yl)-9-azabicyclo[3.3.1]non-2-ene

Oxalate salt, colourless plates, mp 245-257°C (from ethanol); (Found: C, 70.82; H, 6.25; N, 6.61. $C_{23}H_{24}N_2.C_2H_2O_4.H_{0.6}O_{0.3}$ requires C, 70.84; H, 6.33; N, 6.61%); δ_H (360 MHz, d_6-DMSO) 1.50-2.10 (6H, m, aliphatic H), 2.20 (1H, d with other fine coupling, *J* 19, pelletierene H-4'), 2.75 (1H, m, aliphatic H), 2.80 (3H, s, CH_3), 3.60 (1H, m, pelletierene H-1 or pelletierene H-5), 4.10 (1H, m, pelletierene H-5 or pelletierene H-1), 5.80 (1H, d, *J* 5, pelletierene H-2), 7.08 (1H, t, *J* 7, ArH), 7.18 (1H, t, *J* 7, ArH), 7.50 (2H, t, *J* 7, ArH), 7.60 (1H, d, *J* 7, ArH), 7.66 (2H, d, *J* 7, ArH), 11.58 (1H, br s, NH); *m/z* (ES^+) 329 (M^++H).

EXAMPLE 11

endo-3-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-2-phenyl-1*H*-indole and *exo*-3-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-2-phenyl-1*H*-indole

3-(8-Methyl-8-azabicyclo[3.2.1]oct-2-en-3-yl)-2-phenyl-1*H*-indole (0.15 g, 0.48 mmol) was dissolved in trifluoroacetic acid (5 ml) and triethylsilane (0.25 g, 2.15 mmol) added and the reaction mixture heated at 55°C for 36 h. The reaction mixture was basified with saturated potassium carbonate solution and the product extracted into ethyl acetate. The organic layer was washed with water and brine, dried over sodium sulphate and evaporated to dryness. The product was purified by flash column chromatography on silica using dichloromethane/methanol/ ammonia (95:5:0.5) as eluent to yield 3-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2-phenyl-1*H*-indole (49 mg, 32%) the isomers of which were separated by thin layer chromatography to give:

endo-3-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2-phenyl-1*H*-indole: δ_H (400 MHz, $CDCl_3$) 1.70-1.80 (2H, m, tropane H-6, *syn* to indole), 1.90 (2H, t, *J* 13, tropane H-2, *cis* to indole), 2.20-2.35 (5H, m, NCH_3 and tropane H-6, *anti* to indole), 2.45 (2H, m, tropane H-2, *trans* to indole), 3.25-3.35 (2H, m, tropane H-1), 3.40-3.60 (1H, m, tropane H-3), 7.10 (1H, t, *J* 8, ArH), 7.20 (1H, t, *J* 8, ArH), 7.30 (2H, m, ArH), 7.50 (4H, m, ArH), 7.80 (1H, d, *J* 8, ArH), 8.00 (1H, br s, NH). In NOESY experiments, cross peaks were observed between the signals at 3.40-3.50 and 2.25, and a cross peak between the signals at 1.75 and 1.90 was observed; this shows the stereochemistry of the compound to be *endo*. *m/z* (ES^+) 317 (M^++H).

exo-3-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2-phenyl-1*H*-indole: δ_H (400 MHz, $CDCl_3$) 1.60 (2H, m, tropane H-2, *cis* to indole), 1.65 (2H, m, tropane H-6, *syn* to indole), 2.10 (2H, m, tropane H-6, *anti* to indole), 2.40 (3H, s, NCH_3), 2.55-2.65 (2H, m, tropane H-2, *trans* to indole), 3.30-3.35 (2H, m, tropane H-1), 3.35-3.45 (1H, m, tropane H-3), 7.10 (1H, t, *J* 8, ArH), 7.20 (1H, t, *J* 8, ArH), 7.30 (2H, m, ArH), 7.50 (4H, m, ArH), 7.80 (1H, d, *J* 8,

ArH), 8.00 (1H, br s, NH). In NOESY experiments, cross-peaks were observed between the signals at 3.45 and 1.65; this shows the stereochemistry of the compound to be *exo*. *m/z* (ES^+) 317 (M^++H).

EXAMPLE 12

endo-3-(8-Azabicyclo[3.2.1]oct-3-yl)-2-(4-fluorophenyl)-1*H*-indole

Oxalate salt; δ_H (400 MHz, d_6-DMSO) 2.00-2.30 (7H, m, tropane H), 2.30-2.40 (2H, m, tropane H), 4.00-4.20 (2H, m, tropane H-1 and H-5), 7.00-7.10 (1H, m, indole H-5 or H-6), 7.10-7.20 (1H, m, indole H-6 or H-5), 7.30-7.40 (3H, m, indole H and ArH), 7.50-7.60 (2H, m, ArH), 7.60-7.70 (1H, m, indole H-4), 8.60 (1H, br s, indole NH); *m/z* (ES^+) 321 (M^++H).

EXAMPLE 13

endo-3-(8-Azabicyclo[3.2.1]oct-3-yl)-2-(benzo[1,3]dioxol-5-yl)-1*H*-indole

Oxalate salt, white crystals, mp 225-227°C; (Found C, 60.09; H, 5.06; N, 5.63. $C_{22}H_{22}N_2O_2 \cdot 1.5\ (C_2H_2O_4) \cdot H_2O$ requires C, 60.12; H, 5.45; N, 5.61%); δ_H (400 MHz, d_6-DMSO) 2.00-2.20 (6H, m, tropane H), 2.30-2.40 (2H, m, tropane H), 3.40-3.50 (1H, m, tropane H-3), 4.00 (2H, br s, tropane H-1 and H-5), 6.10 (2H, s, methylenedioxy H), 7.00-7.10 (5H, m, ArH), 7.30 (1H, d, *J* 8, indole H-7), 7.60 (1H, d, *J* 8, indole H-4), 8.80 (1H, br s, indole NH); *m/z* (ES^+) 347 (M^++H).

EXAMPLE 14

endo-3-(8-Azabicyclo[3.2.1]oct-3-yl)-6-fluoro-2-(4-fluorophenyl)-1*H*-indole

White crystals, mp 255-256°C (from EtOAc); (Found: C, 73.70; H, 5.88; N, 8.18. $C_{21}H_{22}N_2 \cdot 0.2\ H_2O$ requires C, 73.75; H, 6.01; N, 8.19%); δ_H (360 MHz, d_6-DMSO) 1.70-1.90 (6H, m, tropane H), 2.10-2.20 (2H, m, tropane H-2), 3.20-3.30 (1H, m, tropane H-3), 3.50-3.60 (2H, m, tropane H-

1), 6.85 (1H, dt, *J* 2 and 9, indole H-5), 7.06 (1H, dd, *J* 2 and 10, indole H-7), 7.31 (2H, t, *J* 9, ArH *o* to F), 7.40-7.60 (3H, m, ArH); *m/z* (ES^+) 339 (M^++H).

EXAMPLE 15

endo-2-Phenyl-3-[8-(2-thien-3-yl)ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1*H*-indole

Triethylamine (1 ml, 7.2 mmol), 3-thiopheneacetic acid (210 mg, 1.5 mmol), 1-hydroxybenzotriazole (200 mg, 1.5 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (285 mg, 1.5 mmol) were added to a solution of *endo*-3-(8-azabicyclo[3.2.1]oct-3-yl)-2-phenyl-1*H*-indole (300 mg, 1.0 mmol) in *N,N*-dimethylformamide (5 ml). The mixture was strirred at room temperature for 18 hours, diluted with ethyl acetate (30 ml) and washed with 2 N hydrochloric acid (30 ml), saturated sodium hydrogen carbonate solution (30 ml) and water (30 ml). The organics were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by recrystallisation from dichloromethane and methanol to give 1-[3-(2-phenyl-1*H*-indol-3-yl)-8-azabicyclo[3.2.1]oct-8-yl]-2-(thien-3-yl)ethanone as a pale yellow solid (174 mg, 41%); δ_H (360 MHz, d_6-DMSO) 1.80-2.10 (7H, m, tropane H), 2.70-2.80 (1H, m tropane H-3), 3.60 (2H, q, *J* 15.1, methylene H), 4.30-4.40 (1H, m, tropane H-5 or H-1), 4.50-4.55 (1H, m, tropane H-1 or H-5), 6.80 (1H, d, *J* 4.8, thiophene H-3), 6.90 (1H, t, *J* 7.4, ArH), 7.05-7.15 (2H, m, ArH), 7.20 (1H, m, ArH), 7.30 (1H, d, *J* 8.0, indole H-7), 7.40-7.60 (5H, m, ArH), 7.70 (1H, d, *J* 7.8, indole H-4), 11.00 (1H, s, indole NH). 1 M Borane-tetrahydrofuran complex (13 ml, 13 mmol) was added to a solution of 1-[3-(2-phenyl-1*H*-indol-3-yl)-8-azabicyclo[3.2.1]oct-8-yl]-2-(thien-3-yl)ethanone (170 mg, 0.4 mmol) in dry tetrahydrofuran (30 ml), and the mixture stirred at 50°C for 24 hours. To the cooled mixture was added a solution of hydrochloric acid in methanol (50 ml, 1% v/v solution), stirred at 50°C for 18 hours, concentrated, a

further portion of hydrochloric acid in methanol (50 ml, 1% v/v solution) added, and the mixture stirred for 2 hours at room temperature. The residue was purified by prep-TLC eluting with dichloromethane: methanol:ammonia (90:9:1 w/v) to give the *title compound*: oxalate salt (116 mg, 56%); mp 264-267°C; (Found C, 64.05; H, 6.48; N, 6.34. $C_{27}H_{28}N_2S \cdot C_2H_2O_4 \cdot 2.4\ H_2O$ requires C, 63.81; H, 6.43; N, 5.13%); δ_H (360 MHz, d_6-DMSO) 2.00-2.20 (4H, m, tropane H), 2.40-2.60 (4H, m, tropane H), 3.10 (4H, br s, methylene H), 3.80-3.90 (1H, m, tropane H-3), 4.10 (2H, br s, tropane H-1 and H-5), 7.00-7.15 (3H, m, ArH), 7.30-7.45 (3H, m, ArH), 7.50-7.60 (5H, m ArH), 7.60 (1H, d, *J* 7.8, indole H-4), 11.20 (1H, s, indole NH); *m/z* (ES^+) 413 (M^++H).

EXAMPLE 16

endo-3-[8-(2-(1-Methyl-1*H*-pyrazol-4-yl)ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-phenyl-1*H*-indole

1-Methyl-4-(2-methanesulfonyloxyethyl)pyrazole (203 mg, 0.99 mmol; EP-A-0733628) and potassium carbonate (340 mg, 2.5 mmol) were added to a solution of *endo*-3-(8-azabicyclo[3.2.1]oct-3-yl)-2-phenyl-1*H*-indole (300 mg, 1.0 mmol) in *N,N*-dimethylformamide (15 ml) and the mixture stirred at 100°C for 24 hours. The cooled mixture was poured into water (100 ml) and extracted with ethyl acetate (3 x 50 ml), the combined organics dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography eluting with dichloromethane:methanol (93:7 w/v) to give the *title compound* as a white solid: oxalate salt (31 mg), mp 178-180°C; (Found C, 69.58; H, 6.45; N, 11.00. $C_{27}H_{30}N_4 \cdot C_2H_2O_4$ requires C, 69.52; H, 6.44; N, 11.19%); δ_H (360 MHz, d_6-DMSO) 2.00-2.20 (4H, m, tropane H-6 and tropane H-7), 2.40-2.60 (4H, m, tropane H-2 and tropane H-4), 2.80-2.90 (2H, m, methylene), 3.00-3.10 (2H, m, methylene), 3.60-3.70 (1H, m, tropane H-3), 3.80 (3H, s, NMe), 4.00-4.10 (2H, br s, tropane H-1 and H-5), 7.00-7.20 (2H, m, ArH), 7.30-7.40 (2H, m, ArH),

7.40-7.50 (1H, m, ArH), 7.50-7.60 (5H, m, ArH), 7.70 (1H, d, *J* 7.7, indole H-4), 11.20 (1H, s, indole NH); *m/z* (ES+) 411 (*M*+H).

EXAMPLE 17

1-[2-(3-(2-Phenyl-1*H*-indol-3-yl)-8-azabicyclo[3.2.1]oct-2-en-8-yl)ethyl]-imidazolidin-2-one

1-(2-Chloroethyl)-2-imidazolidinone (100 mg, 0.67 mmol) followed by potassium carbonate (150 mg, 1.1 mmol) and sodium iodide (150 mg) was added to a solution of 3-(8-azabicyclo[3.2.1]oct-2-en-3-yl)-2-phenyl-1*H*-indole (100 mg, 0.33 mmol) in isopropyl alcohol (10 ml). The mixture was refluxed for 18 hours in the dark. The solvent was evaporated and the residue partitioned between water and dichloromethane. The aqueous layer was extracted with dichloromethane and the combined organics dried and evaporated. The residue was purified by column chromatography on silica eluting with dichloromethane:methanol to give a white foam (130 mg, 94%); oxalate salt mp >185°C (decomp); (Found: C, 64.24; H, 5.80; N, 10.61. $C_{26}H_{28}N_4O \cdot 1.38(CO_2H)_2$ requires C, 64.38; H, 5.78; N, 10.45%); δ_H (400 MHz, d_6-DMSO, 350°K) 1.89-1.98 (1H, m, aliphatic H), 2.17 (1H, d, *J* 16, tropane H-4), 2.22-2.42 (3H, m, aliphatic H), 2.87 (1H, d, *J* 16, tropane H-4'), 3.18-3.29 (2H, m, aliphatic H), 3.29-3.37 (2H, m, aliphatic H), 3.40-3.50 (4H, m, aliphatic H), 3.95-4.05 (1H, m, aliphatic H), 4.20-4.29 (1H, m, aliphatic H), 5.97 (1H, d, *J* 6, tropane H-2), 7.03-7.09 (1H, m, ArH), 7.12-7.18 (1H, m, ArH), 7.37-7.43 (2H, m, ArH), 7.48-7.55 (2H, m, ArH), 7.58-7.68 (3H, m, ArH), 11.56 (1H, s, NH); *m/z* (ES+) 413 (*M*+H).

EXAMPLE 18

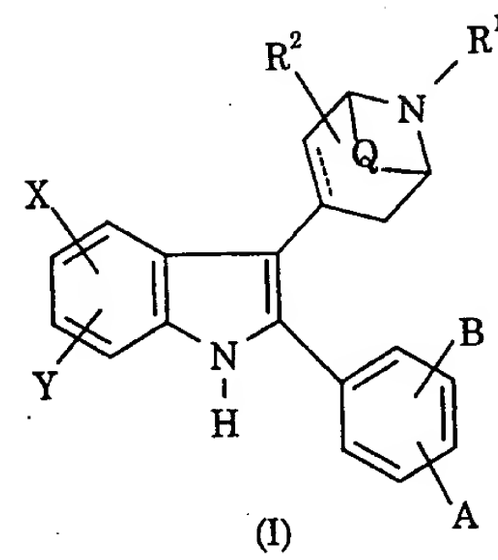
3-(8-Aza-2-hydroxybicyclo[3.2.1]oct-3-yl)-2-phenyl-1*H*-indole

3-(8-Azabicyclo[3.2.1]oct-2-en-3-yl)-2-phenyl-1*H*-indole (2.2 g), di-*tert*-butyldicarbonate (1.9 g) and triethylamine (1.4 ml) were stirred in dichloromethane (20 ml) for 24 h then *N*,*N*-dimethylethylenediamine (1 ml) added, and the solution stirred for a further 1 h. The mixture was evaporated, ethyl acetate (50 ml) added, and the solution washed with dilute citric acid solution, water and brine, dried and evaporated to give a brown foam (2.38 g). 1 g of this foam was dissolved in THF (2.5 ml) at 0°C, then borane-dimethylsulfide complex (2.5 ml, 2 M in THF) added. After 1 h the mixture was warmed. Borane-dimethylsulfide complex (1 ml, 2 M in THF) was added and the mixture kept at room temperature for 24 h. A further portion of borane-dimethylsulfide complex (1 ml, 2 M in THF) was added and the mixture kept at room temperature for 24 h. Sodium hydroxide (4 M, 5 ml) then hydrogen peroxide (30%, 5 ml) was added, and the mixture stirred for 6 h. Ethyl acetate was added, and the mixture washed with water and brine, dried, evaporated and purified by flash chormatography, eluting with hexane:ethyl acetate (4:1 v/v) to give a white foam (0.65 g). 100 mg of this foam was dissolved in ethyl acetate (1 ml) and a saturated solution of HCl in ether (5 ml) added. After 4 h at room temperature, ethyl acetate and sodium hydrogen carbonate solution were added, separated, and the organic layer washed with water and brine, dried and evaporated. Dichloromethane (1 ml) was added, on which the product (61 mg) crystallised as white crystals, mp 154-155°C; (Found: C, 71.07; H, 6.43; N, 7.67. $C_{21}H_{22}N_2O \cdot HCl$ requires C, 71.08; H, 6.53; N, 7.89%); δ_H (400 MHz, d_6-DMSO) 1.43 (1H, dd, *J* 12.9 and 12.9, tropane H-4), 1.50-1.55 (1H, m, tropane H-6), 1.60-1.65 (1H, m, tropane H-6'), 1.75-1.80 (1H, m, tropane H-7), 1.80-2.00 (2H, m, tropane H-4' and 7'), 3.00-3.10 (1H, m, tropane H-3), 3.32 (1H, d, *J* 9, tropane H-1), 3.42 (1H, dd, *J* 6 and 9, tropane H-5), 3.83 (1H, dd, *J* 4.7 and 9, tropane H-2), 4.79 (1H, d, *J* 4.7,

OH), 6.97 (1H, t, *J* 7, ArH), 7.06 (1H, t, *J* 7, ArH), 7.20-7.60 (4H, m, ArH), 7.76 (1H, d, *J* 8, indole H-4), 11.00 (1H, s, indole NH); *m/z* (ES^+) 319 (M^++H).

CLAIMS:

1. A compound of formula I, or a salt thereof:



(I)

wherein the broken line represents an optional chemical bond;

A and B independently represent hydrogen, halogen, cyano, nitro, trifluoromethyl, trifluoromethoxy, C_{1-6} alkyl or C_{1-6} alkoxy; or A and B, when attached to adjacent carbon atoms, together represent methylenedioxy;

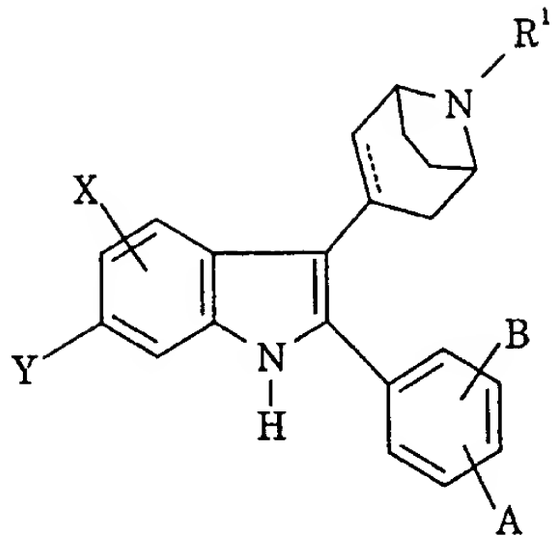
X and Y independently represent hydrogen, halogen, trifluoromethyl, trifluoromethoxy, C_{1-6} alkyl, C_{1-6} alkoxy or phenyl;

Q represents a group of formula $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$;

R^1 represents hydrogen, C_{1-6} alkyl, or an optionally substituted aryl(C_{1-6})alkyl, heteroaryl(C_{1-6})alkyl or C_{3-7} heterocycloalkyl(C_{1-6})alkyl group; and

R^2 represents hydrogen, halogen, C_{1-6} alkyl, hydroxy or C_{1-6} alkoxy.

2. A compound as claimed in claim 1 represented by formula II, and salts thereof:



(II)

wherein

A, B, X, Y, R^1 and the broken line are as defined in claim 1.

3. A compound selected from:

3-[8-(2-phenylethyl)-8-azabicyclo[3.2.1]oct-2-en-3-yl]-2-phenyl-1*H*-indole;

endo-3-[8-(2-phenylethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-phenyl-1*H*-indole;

endo-3-(8-azabicyclo[3.2.1]oct-3-yl)-2-phenyl-1*H*-indole;

3-(8-azabicyclo[3.2.1]oct-2-en-3-yl)-2-phenyl-1*H*-indole;

3-(8-methyl-8-azabicyclo[3.2.1]oct-2-en-3-yl)-2-phenyl-1*H*-indole;

3-(8-azabicyclo[3.2.1]oct-2-en-3-yl)-6-fluoro-2-phenyl-1*H*-indole;

3-(8-azabicyclo[3.2.1]oct-2-en-3-yl)-6-fluoro-2-(3-fluorophenyl)-1*H*-indole;

3-(8-azabicyclo[3.2.1]oct-2-en-3-yl)-6-fluoro-2-(4-fluorophenyl)-1*H*-indole;

3-(8-azabicyclo[3.2.1]oct-2-en-3-yl)-2-(4-fluorophenyl)-1*H*-indole;

3-(8-azabicyclo[3.2.1]oct-2-en-3-yl)-2-(benzo[1,3]dioxol-5-yl)-1*H*-indole;

9-methyl-3-(2-phenyl-1*H*-indol-3-yl)-9-azabicyclo[3.3.1]non-2-ene;

endo-3-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2-phenyl-1*H*-indole;

exo-3-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2-phenyl-1*H*-indole;

endo-3-(8-azabicyclo[3.2.1]oct-3-yl)-2-(4-fluorophenyl)-1*H*-indole;

endo-3-(8-azabicyclo[3.2.1]oct-3-yl)-2-(benzo[1,3]dioxol-5-yl)-1*H*-indole;

endo-3-(8-azabicyclo[3.2.1]oct-3-yl)-6-fluoro-2-(4-fluorophenyl)-1*H*-indole;

endo-2-phenyl-3-[8-(2-(thien-3-yl)ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1*H*-indole;

endo-3-[8-(2-(1-methyl-1*H*-pyrazol-4-yl)ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-phenyl-1*H*-indole;

1-[2-(3-(2-phenyl-1*H*-indol-3-yl)-8-azabicyclo[3.2.1]oct-2-en-8-yl)ethyl]-imidazolidin-2-one;

3-(8-aza-2-hydroxybicyclo[3.2.1]oct-3-yl)-2-phenyl-1*H*-indole;

and salts thereof.

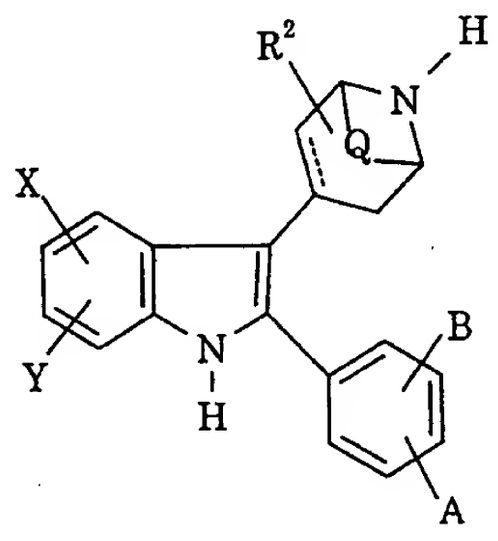
4. A pharmaceutical composition comprising a compound of formula I as defined in claim 1 or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable carrier.

5. A composition as claimed in claim 4 further comprising another anti-schizophrenic medicament.

6. The use of a compound of formula I as defined in claim 1 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment and/or prevention of psychotic disorders.

7. A process for the preparation of a compound as claimed in claim 1, which comprises:

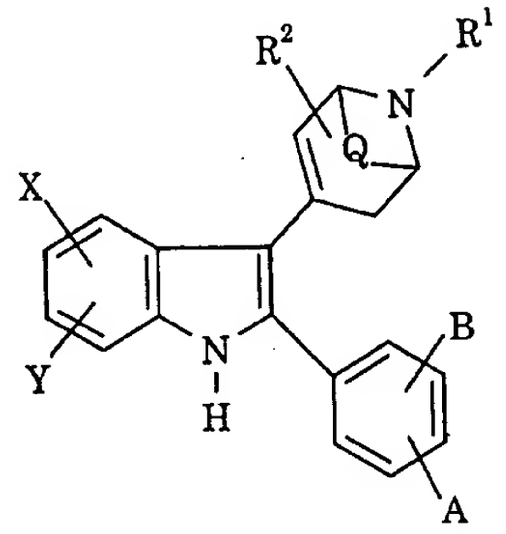
(A) attachment of the R^1 moiety to a compound of formula III:



(III)

wherein A, B, X, Y, Q, R^2 and the broken line are as defined in claim 1; or

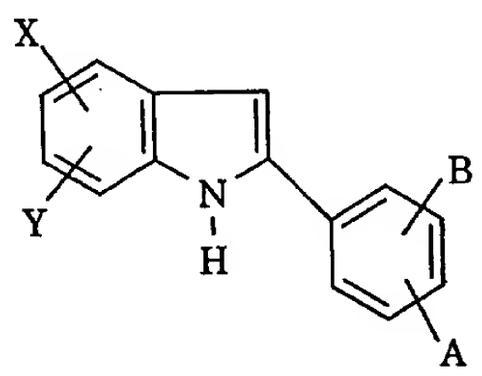
(B) reducing a compound of formula V:



(V)

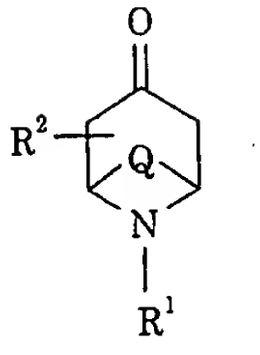
wherein A, B, X, Y, Q, R^1 and R^2 are as defined in claim 1; or

(C) reacting a compound of formula VI:



(VI)

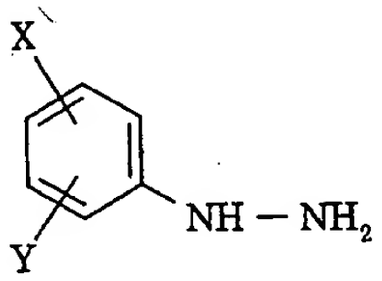
wherein A, B, X and Y are as defined in claim 1; with a compound of formula VIII:



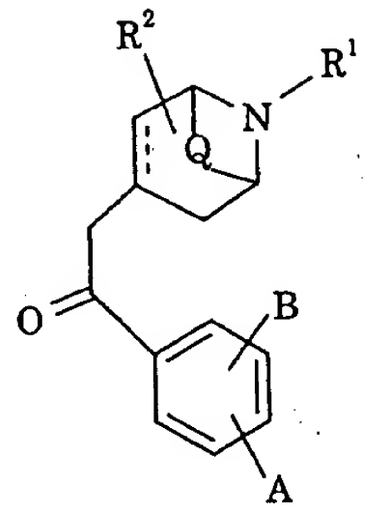
(VIII)

wherein Q, R^1 and R^2 are as defined in claim 1; or

(D) reacting a compound of formula IX or an acid addition salt thereof with a compound of formula X:



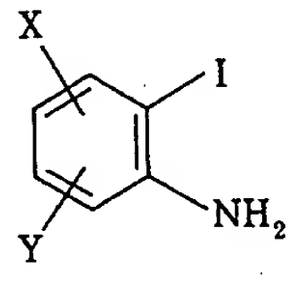
(IX)



(X)

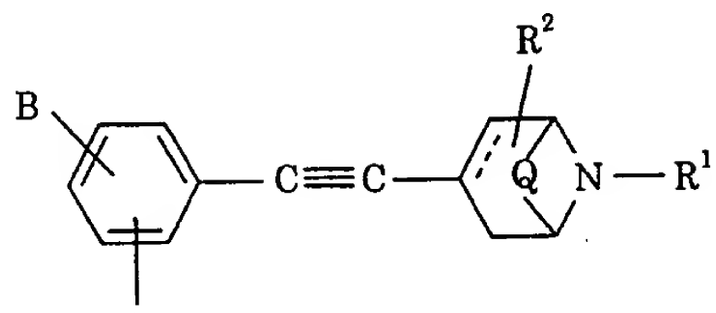
wherein A, B, X, Y, Q, R^1, R^2 and the broken line are as defined in claim 1; or

(E) reacting a compound of formula XI



(XI)

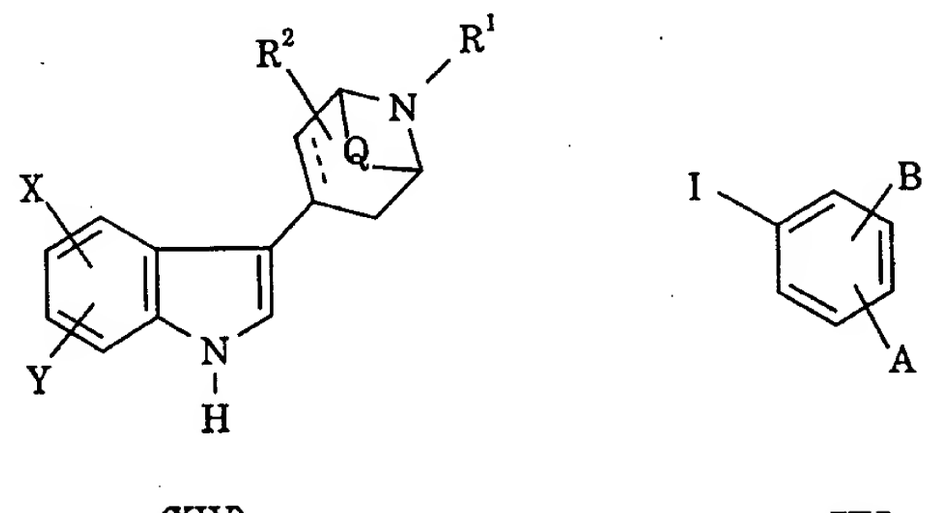
wherein X and Y are as defined in claim 1; with a compound of formula XIII:



(XIII)

wherein A, B, Q, R^1, R^2 and the broken line are as defined in claim 1; in the presence of a transition metal catalyst; or

(F) reacting a compound of formula XIV with a compound of formula XV:



(XIV)

(XV)

wherein A, B, X, Y, Q, R^1, R^2 and the broken line are as defined in claim 1; in the presence of a transition metal catalyst; and

(G) subsequently, where required, converting a compound of formula I initially obtained into a further compound of formula I by conventional methods.

8. A method for the treatment and/or prevention of psychotic disorders which comprises administering to a patient in need of such treatment an effective amount of a compound of formula I as defined in claim 1 or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/GB 99/02177

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D451/02 A61K31/46 C07D451/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 747 379 A (ADIR ET COMPAGNIE) 11 December 1996 (1996-12-11) claim 1; examples 11,12	1,4,6
A	EP 0 465 398 A (H. LUNBECK A/S) 8 January 1992 (1992-01-08) page 5; claim 1	1,4,6

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 October 1999	08/11/1999
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Van Bijlen, H

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

	International application No.
	PCT/GB 99/02177

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 8
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim 8 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 99/02177

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